

Mid-life reversibility of early-established biobehavioral risk factors: a research agenda

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Abstract

Objectives: Epidemiological evidence links exposure to early life adversities --such as childhood maltreatment-- with impaired health and wellbeing in adulthood. Since these effects are usually unrecognized or untreated in childhood, preventive and remediating interventions in adults are needed. We asked, first, can we validly ascertain childhood adversity through retrospective assessments in adulthood? Second, what dimensions of childhood adversity have consequences for adult health? Third, is there enough plasticity in adult behaviors and neural function in mid-life to allow for interventions?

Methods: Supported by the National Institute on Aging, the UK Economic and Social and the Biotechnology and Biological Sciences Research Councils, a network of researchers in human and animal development addressed these questions through meetings and literature review.

Results: Widely-used adult ascertainties of childhood adversity are poorly related to prospective ascertainment. A small number of dimensions may adequately distinguish among a range of co-occurring childhood adversities and early childhood periods of sensitivity to environmental influence might be reopened in adulthood to favor preventive interventions.

Discussion: Prospective animal and human research is clarifying targets for intervention to prevent ill health while subgroups of adults who believe they had adverse childhoods, whether or not that was the case, may require special intervention for effective treatment of established illness.

Keywords not in title: Preventive intervention, child maltreatment, retrospective ascertainment,

Early life adversities (ELAs) come in many forms, including poverty, life in depriving orphanages, nutritional deficiency in utero and beyond, deficiencies in parental nurturing, various forms of maltreatment, and loss of a parent or other attachment figure. A more recent line of research explores the distinctive and long term effects of racism early in development (e.g., Chae et al., 2018; Pachter & Coll, 2009). Human and animal research has established that ELAs engender a liability for ill health (i.e., they are related to later outcomes, though there is not yet clear evidence of a causal link) that persists through mid-life. While there are interventions for children that offset some of this risk, there are fewer interventions to counter this liability in adults. A coordinated effort to develop interventions for adults is urgent. Future research will be aided by clearer conceptualization and measurement of ELA as well as delineation of useful strategies for targeting and ameliorating risk mechanisms linking ELA to adult health. We briefly summarize evidence underscoring the importance of ELA in adult health. Then we review several approaches to conceptualizing and measuring ELA and discuss the relative advantages and disadvantages of retrospective and prospective ascertainment of ELA. Following, we outline two broad strategies for further research on useful interventions. In one of these, recalled ELA helps to anticipate malignant course and resistance to treatment in established illness, suggesting the existence of clinical subtypes that may benefit from targeted intervention. In a second, information on ELA is useful for identifying disease liability and planning prevention efforts prior to disease onset. Finally, we address the practical challenge of designing prevention trials for health outcomes that only become apparent years or decades in the future and consider recent research that may provide valid intermediary outcomes for rigorous efficacy testing.

The systematic study of the impact of ELA on adult mental and physical health gained momentum a half century ago (e.g., Berkman, 1971; Forsdahl, 1978; Kiernan, Colley, Douglas, & Reid, 1976). Throughout, the definition of ELA has been broad and has ranged from general indices of adversity such as social class to more specific exposures of fetuses or children to malnutrition and maltreatment from caretakers. As we will note below, there is recent progress in more coherent and empirical based ascertainment of ELA.

Two landmark studies have galvanized this field. The first was the discovery of links between ELA and health at mid-life that came from fastidious records of birth weights compiled by midwives in Hertfordshire, England, to assure proper childhood nutrition after a large number of men failed eligibility to fight in the Boer War (Barker, 2003). Over 60 years later, David Barker and colleagues used these records to report an association between low birth weight and deaths from coronary heart disease decades later. Numerous follow-up studies confirmed this startling observation (e.g., Eriksson et al., 1999), and experimental studies with animals using nutritional challenges (e.g., Fleming et al., 2018) and fetal growth restriction (e.g., Schreuder, Fodor, van Wijk, & Delemarre-van de Waal, 2006) suggested that these associations between diminished fetal growth and cardiac disease were causal and documented mechanisms accounting for them. In a second notable study, Felitti and colleagues investigated the relationship of postnatal adverse childhood experiences (ACEs) recalled by adults, including the physical and psychological abuse they experienced as children. They observed substantial associations between the number of ACEs recalled and the prevalence of risky health behaviors, such as drug abuse, and of cardiometabolic diseases and cancer in mid-life (Felitti et al., 1998). The Barker studies were a model of clear conceptualization of an ELA and the deft integration of human and animal prospective studies to establish causal pathways via risk mechanisms linking

ELA and adult disease. The Felitti study yielded an easily administered questionnaire, suitable for large samples, that provide replicable results linking recalled adversity with current and future health.

More recently, several prospective studies of the long-term effects of ELA have assessed childhood exposures using multiple contemporaneous sources including agency records, in order to identify children exposed to ELA and compare their health trajectories to those of children without known adversity. Some investigators have followed such children to mid-life. These studies have, for example, reported associations between several types of ELA, including severe maltreatment, with adult maladaptive social, behavioral, and health outcomes, especially: 1) emerging risk factors for a range of medical illnesses, including chronic inflammation, elevated hemoglobin A1c, and respiratory compromise (e.g., Danese et al., 2009; Power & Hertzman, 2007; Widom, Czaja, Bentley, & Johnson, 2012)¹; 2) risky behaviors, such as prostitution and illicit drug use (Widom & Kuhns, 1996; Wilson & Widom, 2009); 3) impaired economic well-being (Currie & Widom, 2011), and 4) abusive parenting that may perpetuate adversity across generations (Widom, Czaja, & DuMont, 2015). Animal studies that model adverse social exposures in controlled experiments, using strategies akin to those on fetal growth restriction, provide evidence that supports many of these human findings (e.g., Conti et al., 2012; Maestripieri, Lindell, & Higley, 2007). Felitti's ACEs questionnaire, given to a large sample of adults, has also predicted major health outcomes later in their life including all-cause mortality over a ten-year follow-up period. There was a clear threshold effect: only those with six or more recalled adversities showed a notable effect (Brown et al., 2009)

¹ Danese et al relied in part on retrospective reports when the children became adults but predicted health consequences over a decade later. Widom used only records of child protective services.

Several successful interventions have been developed for children and their families to mitigate the impact of ELAs on relatively short-term, mental health outcomes (e.g., Toth, Gravener-Davis, Guild, & Cicchetti, 2013). Some, with long-term follow-ups, demonstrate impacts on adult cardiometabolic health (Campbell et al., 2014). However, even in those very few countries that carefully monitor childhood adversities and, also, have resources to intervene to prevent its long-term consequences, there will be many individuals who are neither recognized nor treated. They will arrive in adulthood with significant disease liabilities, but with no evidence-based interventions available to reverse or compensate for these risks and enhance their potential for achieving good health in older age.

The US National Institute on Aging (NIA) and the UK Economic and Social Research Council (ESRC) and Biotechnology and Biological Sciences Research Council (BBSRC) recognized the need to explore the potential for such preventive interventions because: 1) ELAs are highly prevalent (Wildeman et al., 2014)—as high as 20% prevalence of maltreatment in some US subpopulations (using very conservative ascertainment based only on records of child protective services); 2) the magnitude of associations between ELAs and adult health is substantial; 3) adversities, as noted, are associated with a broad range of impairments in adult well-being and health, and 4) emerging evidence suggests that many of the observed associations may be causal. Accordingly, the NIA and ESRC/BBSRC supported a group of senior scientists in the Interdisciplinary Network on Early Adversity and Later Life Reversibility. Below, we describe a series of next steps in research—recommended by the Network—to advance this agenda, beginning with evidence-based consensus on clearest conceptualization and best ascertainment of ELAs.

Conceptualizing and measuring ELA

A major question facing researchers is what adversities they should ascertain and what methods of ascertainment are most reliable and valid. To address this and related questions the Network identified seven major research questions to address as crucial to the next generation of research.

1) Do all early adversities have approximately the same impact on adult health and can they be cumulated into an aggregate adversity score?

In their influential work, Felitti and colleagues asked adults about a number of adverse exposures and simply added these up, weighting each item equally. Their underlying assumption was that different adversities have similar effects, and that effects on a broad range of health outcomes are cumulative: the more you recall, the more likely you are to fall ill (Felitti 1998). Recent work has confirmed the utility of this approach in predicting mental health outcomes associated with various forms of prospectively measured maltreatment collected contemporaneously in childhood (Vachon, Krueger, Rogosch, & Cicchetti, 2015). However, the limits of this approach will become apparent if future research establishes that particular adversities have specific long-term effects on adults. For example, Geoffroy and colleagues showed that childhood neglect anticipated cognitive deficits in adults, but childhood abuse did not (Geoffroy, Pinto Pereira, Li, & Power, 2016). Moreover, as we note below, there are many forms of early life adversity that are not indexed by the Felitti measure.

2) Can ELAs be grouped according to their distinctive effects both on risk mechanisms and health outcomes?

Research now explores whether distinct dimensions of adversity have differential impacts on the brain, biology, and health outcomes. For example, McLaughlin and colleagues (2014)

have proposed two. First, deprivation – the lack of social and cognitive stimulation important for normal brain development -- is conspicuous in children in extended care in poorly run institutions. McLaughlin and colleagues suggest that deprivation has consequences for development of the cortex in frontal and temporal lobes and is associated with deficits in language and cognitive function. Second, threat is a central feature of physical and sexual abuse. Mediated through activation of the HPA axis, studies of animals exposed to early life threat reveal anatomical and functional changes in hippocampus, amygdala, and ventromedial prefrontal cortex with impaired fear extinction learning (McLaughlin, Sheridan, & Lambert, 2014). In humans, heightened amygdala activity to threatening stimuli has been demonstrated in children exposed to family violence, suggesting a distinct neural signature of heightened threat sensitivity (McCrory et al, 2011). Distinguishing between deprivation and threat and their related psychological and physiological effects holds potential for elucidating differential pathways through which exposures become biologically embedded, leading to variations in later health outcomes, as seen for example with cognition and mental health (Geoffroy et al., 2016).

Other potential dimensions that may group some events together for impact on health include unpredictability in the child's environment, for example, in parental behavior, residential location, co-habitation, or employment status. Unpredictability has been modeled in animals and is associated with impaired development in human studies (e.g., Baram et al., 2012; Simpson, Griskevicius, Kuo, Sung, & Collins, 2012). Loss – through death or separation from an attachment figure--particularly from parents, is an ordinal dimension of ELA that may have distinct effects and, importantly, has been associated with a range of psychiatric disorders independent of genetic effects (Kendler, Neale, Kessler, Heath, & Eaves, 1992).

Research has explored whether poverty has a distinct effect, immediate or delayed, on children's health, independent of other dimensions with which it is often associated such as maltreatment. Support for the causal effects of poverty comes from a natural experiment (the opening of a casino on a Native American reservation) and a planned experiment (voucher support to poor families allowing a move into a better neighborhood) that both improved the mental health and economic productivity of children, an effect sustained into adulthood (Chetty, Hendren, & Katz, 2016; Costello, Erkanli, Copeland, & Angold, 2010). A growing number of studies suggest that the conditions that may accompany early life poverty, including lack of cognitive stimulation, undernutrition, maternal stress, or insufficient parental nurturing, may have long-term effects on neural and psychological development (Eisenberg et al., 2007; Farah et al., 2006; Hackman, Farah, & Meaney, 2010; Noble et al., 2015). Well-documented associations between early life adversity, educational attainment and cognitive health, are driving current efforts to elucidate the causal pathways accounting for these associations (National Institute on Aging, 2016; Power & Hertzman, 1997) including efforts to ascertain the extent of genetic influences on these associations (Krapohl & Plomin, 2016). Finally, as noted above, fetal undernutrition, often associated with poverty, has significant long-term consequences for adult health but postnatal undernutrition does as well (Tennant et al., 2014). Research is urgently needed to improve measurement of each of these proposed dimensions to test whether they clarify mechanisms linking childhood exposures to adult health, and to ascertain whether they have distinctive effects on long-term outcomes or lead to similar outcomes via different causal pathways.

3) Does moderate adversity promote resilience?

Dimensions of adversity exposure may not be monotonically related to unfavorable health outcomes. Moderate levels of adversity in childhood may “steel” individuals against adversities later in life, a phenomenon known in some research fields as stress inoculation, demonstrated in animal models and with preliminary evidence in humans (Liu, 2015). For example, experimentally controlled brief separation of squirrel monkey offspring from their mothers led, in follow-up, to enhanced cognitive control and exploratory behavior in the offspring (see review: Lyons, Parker, & Schatzberg, 2010). In young human adults, for example, exposure to family conflict in early life has a curvilinear relationship with HPA axis reactivity, measured in response to a laboratory interpersonal conflict paradigm, suggesting that moderate levels of early life stress have a buffering effect on subsequent stress reactivity (Hagan, Roubinov, Purdom Marreiro, & Luecken, 2014)

4) Are there periods in development where children show heightened sensitivity to particular adversities?

ELAs occurring in critical or sensitive periods – when developing systems are plastic and particularly sensitive to environmental inputs - may have enduring effects on liability for non-communicable diseases later in development. It has been proposed that these early exposures prime or “program” systems within the fetus or infant to anticipate characteristics of the subsequent environment to which they will be exposed (Godfrey & Barker, 2001). According to this view, adverse exposures during critical periods result in irreversible changes; if the environment in later childhood and adult life differs from that “predicted” during fetal life and infancy, the developmental responses may increase the risk of adult disease. Broad categories of adverse exposure that induce developmental responses of this kind include maternal obesity (Godfrey et

al., 2017), micronutrient deficiency (Lin et al., 2017), and stress as early as preconception (El-Heis et al., 2017), as well as during pregnancy and early postnatal periods (Wen et al., 2017).

As a complement to models of fetal and infant programming, Power and Hertzman (1997) articulate a pathways model whereby ELA is linked to health outcomes by a series of sequentially contingent life experiences. For example, in their study of the 1958 British cohort, they found that social class at birth was linked to a range of health outcomes, but the links were stronger for educational attainment, which was partially contingent on - but not equivalent to - social class at birth. Unlike critical period mechanisms, which suggest the need for intervention efforts at precise times in early development, pathway models suggest the potential of interventions at later stages of the life span to offset or moderate one or more of the contingent sequential adversities associated with ELA, a topic we explore further below. Current evidence suggests that both processes are at play, and consideration of both fetal programming and pathways models is essential for understanding constraints on later life plasticity and for selection of targets for later life intervention.

5) Do characteristics of the child play a role?

It is clear that the impact of ELAs on long term development can be moderated by child characteristics such as coping strategies (Chen, Miller, Lachman, Gruenewald, & Seeman, 2012), as well as a broad range of factors with a heritable component, such as verbal intelligence (Bagley & Mallick, 2000), and even, according to preliminary evidence, specific polymorphisms of the child (e.g., Cicchetti, Rogosch, Sturge-Apple, & Toth, 2010). However, some conceptualizations of ELA suggest that parental harsh treatment and even abuse may be influenced by difficult or challenging characteristics of the child. There is substantial evidence, for example, that children with physical, neurological, or behavioral abnormalities are at

increased risk of abuse (Jones et al., 2012). Weaker evidence suggests a role of difficult child temperament (e.g., Mackenzie, Nicklas, Brooks-Gunn, & Waldfogel, 2011). Most arresting are studies suggesting heritable characteristics of children may evoke harsh parenting (Jaffee et al., 2004) and even more severe maltreatment (Schulz-Heik et al., 2010). Thus, harsh parenting or frank maltreatment may reflect, in some cases, an escalating transaction between parents made vulnerable by their own risk factors and evocative characteristics of children. We have already noted another transactional model: where there is mismatch between the environment that is sampled by the fetus in utero (or by the young child in adverse social environment) and the environment encountered later in life.

6) Can we identify among children exposed to severe adversity those who are most likely to suffer consequent long-term health problems?

Early indicators of biological embedding of ELA may permit identification of resilient children and the mechanisms of that resilience, of factors that may determine the collapse of this resilience later in development; and may represent the earliest indicators of the impact of ELA on subsequent psychobiological processes that accelerate disease processes. These indicators help improve precision ascertainment of health risks attributable to ELA, before disease processes take hold.

The allostatic load model proposed by McEwen and Seeman (McEwen, 1998; McEwen & Seeman, 1999), articulates how multiple or excessive “hits” to systems that serve to maintain homeostasis and promote health in the face of normal day-to-day challenge, can become dysregulated under severe or cumulative adversity. To maintain homeostasis, stress activates the autonomic and central nervous systems that, in turn, influence cortisol, adrenalin, the immune system, and metabolism. Severe and unrelenting challenges to these systems can result in gradual

and long-term dysregulation in these homeostatic processes, causing them to become overused and dysregulated, resulting in allostatic load and overload (McEwen, 2004). Several approaches have been used to cumulate indices of systems affected, including those based on assays of urinary cortisol, norepinephrine and epinephrine, dyslipidemia, blood pressure, and waist-hip ratio, validated through prediction of future health and mortality (Seeman, McEwen, Rowe, & Singer, 2001).

Adults with a documented history of maltreatment show evidence of high allostatic load (Widom, Horan, & Brzustowicz, 2015). Allostatic load is also manifested in children exposed to severe adversity (Evans, 2003). One component of this load, serum cholesterol, may be elevated in the short term in children with ELA but decline to levels below children without ELA (e.g. Trickett, Noll, Susman, Shenk, & Putnam, 2010). Indeed, *low* serum cholesterol has been reported in some children exposed to ELA who go on to develop psychiatric difficulties (Laurent et al., 2013; White et al., 2017).

More recently, gene expression profiles have been shown to be sensitive to adverse rearing conditions in animals (Meaney, 2001) and humans (Miller et al., 2009). Animal studies suggest that effects of maternal deprivation on offspring gene methylation profiles can be observed in the first month postpartum (Massart, Nemoda, et al., 2016). Effects of prenatal stress in mothers on gene expression profiles in the developing fetus are apparent in both human (Monk et al., 2016) and monkey placentas (Massart, Suderman, et al., 2016).

Models of ELA, such as those of McLaughlin and colleagues (2014), may widen the scope of search for initial indicators. For example, early indicators of biological embedding in children suffering from ELAs that deprives them of cognitive and social stimulation might include reduced cerebral cortical thickness and performance deficits on complex cognitive tasks.

An equally strong case for “psychosocial embedding” can also be made. There is good evidence that child maltreatment, for example, is prospectively associated with children’s problems in emotion regulation, impaired attachment security, withdrawal from or aggression with peers, school problems as well as personality problems, cognitive deficits and both internalizing and externalizing behavioral problems (for a comprehensive review see: Cicchetti & Toth, 2016). These childhood difficulties may help identify children who were both exposed to adversity and are increased risk for later problems. In addition, some of these behavioral or relational problems might reflect a causal path connecting early adversity to health outcomes in mid-life. For example, attachment insecurity in infancy and toddlerhood anticipates cardiorespiratory disease and diabetes at age 32 (Puig, Englund, Simpson, & Collins, 2013).

For both indicators of biological and psychosocial embedding it remains an important research task to determine their persistence into adulthood. Is there a marker that accurately identifies the subgroup of adults with a history of ELA who are vulnerable to later health impairments that are not yet apparent? Beyond identifying this subgroup, there is a broader problem of whether we—at the current state of our knowledge—can validly identify adults who have been exposed to ELAs, whether or not such exposure renders them vulnerable.

7) Can we ascertain in adults their exposure to adversity when they were children?

Most of what we know about the links between ELAs and adult health derives from studies using retrospective recall through questionnaires or structured interviews. In most cases, with notable exceptions (e.g., Barnes, Noll, Putnam, & Trickett, 2009), these procedures have only been validated against other adult ascertainment such as detailed clinical interviews (e.g., Bernstein et al., 1994; Bifulco, Bernazzani, Moran, & Jacobs, 2005; Wingenfeld et al., 2011) or with each other (e.g., Wingenfeld et al., 2011). Recent efforts have focused on the relationships

between retrospective and prospective measures of ELA, including agency reports, on children in long-term longitudinal studies. Published reports (Reuben et al., 2016; Newbury et al., 2018) and the Network's review of 15 additional published studies (Network on Reversibility, 2016) that used both prospective, contemporaneous ascertainment and retrospective recall decades later, suggest poor agreement between the two, with kappas in the low .30s or less, with the exception of reports of parental loss. In the published data by Reuben and colleagues, there were adults who both over-reported and others who under-reported events that were recorded in childhood, with a preponderance of the former.

There is some evidence that current prospective and retrospective measures may be measuring somewhat different constructs. For example, those who recall adversity, in comparison to those prospectively ascertained, score higher on measures of neuroticism, lower on agreeableness (Reuben et al., 2016), and higher on perceived pain (Raphael, Widom, & Lange, 2001)², providing preliminary evidence that retrospective recall may be associated with an individual's high reactivity to physical and emotional stimuli. Recalled childhood adversity is also partly heritable, further evidence that those reports may reflect, in part, dispositional differences among subjects that affect their recall (South, Schafer, & Ferraro, 2015)³. Still, the reported kappas are significantly greater than zero; hence, child adversity may be a considered one of several determinants of adult retrospective reports.

Meanwhile, prospective measures cannot be considered foolproof. Agency reports, for example, have two biases. First, agencies may conclude that a child is maltreated because other

² However, a prospective study—using other indices of early adversity—reported a predictive association with pain (Jones, Power, & Macfarlane, 2009)

³ Prospective ascertainment can also show genetic influence but for different reasons: they reflect the impact on parental maltreatment of heritable, evocative features in the child (Schulz-Heik et al., 2010) rather than on the disposition of the adult who recalls adversity.

members of the family, by their antisocial behavior, have given the child's family a bad reputation. Second, many severely maltreated or traumatized children are never detected by relevant agencies; some may end up in the comparison groups of studies using prospective case identification, thus confounding results unless they are detected by the researcher (Shenk, Noll, Peugh, Griffin, & Bensman, 2016). Third, comparisons between prospective and retrospective measures in the same sample—to be broadly persuasive—must reflect scientific consensus that both the prospective and retrospective measure are aimed at the same construct. Fourth, retrospective measures—especially when they are improved—are often the sole source of data in many large, representative samples of adults and often reveal associations similar to those seen with prospective measures, as demonstrated for both economic outcomes (Currie & Widom, 2011; Pinto Pereira et al., 2017) and HbA1c (Thomas et al., 2008; Widom, Czaja, Bentley, & Johnson, 2012). These population samples are crucial for understanding the causal role of ELA in adult health, the factors that moderate its impact, and the identification of potential beneficiaries of adult interventions.

The striking predictive capability of retrospective measures opens the search for causal relationships and mechanisms between memories of ELA and adult health. That is, causal models would begin with recalled memories of ELA earlier in development and link these to disease incidence later in development. Once this sequence was established these models would seek mediating links between these two, including psychological and behavioral processes, as well as biological mechanisms. These models would acknowledge that several factors determine the content of these memories including--as noted—personality, pain thresholds as well as actual early exposure. As an example of the discovery of a mediating process, the prospective association of the ACEs questionnaire with lung cancer appears partly attributable to increased

smoking among those recalling adverse childhoods (Brown et al., 2010). Future research may establish more detailed biological mechanisms linking recalled ELA and illness incidence. For example, recalled ELA has been associated with general indices of cellular senescence such as telomere shortening (Puterman et al., 2016), known risk factors for subsequent illness such as chronic inflammation (e.g., Miller & Raison, 2016), and brain changes that may be the basis of a broad range of maladaptive behaviors (McCrory, De Brito, & Viding, 2011).

Research efforts to improve retrospective ascertainment are warranted. Improvements might come from the development of structured interviews to replace questionnaires (Barnes et al., 2009). A second approach, building on basic memory research, uses strategies to recreate contexts of adversity, e.g., pictures of sites where adversity may have occurred (Goodman & Melinder, 2007; Memon, Meissner, & Fraser, 2010). A third approach is a search for behavioral patterns (e.g., Kumsta et al., 2015; Shaffer & Sroufe, 2005), distinctive gene expression profiles (e.g., Provençal et al., 2012), markers of chronic inflammation (e.g. Miller et al., 2009), or neurobiological markers (e.g., Gee et al., 2013) that—in combination—are sensitive to ELA. In order to identify adults who might benefited from preventive intervention, research is needed to establish sensitivity and specificity of these adult indices and their persistence into midlife. Inevitably, the criterion for this work on adult ascertainment is the best possible prospective ascertainment of adversity at the time it occurs in long-followed cohorts of exposed children and controls.

Strategies for research on preventive intervention

Based on the best evidence available, the Network anticipated two productive avenues for research on prevention. The first capitalizes on a large volume of data derived from studies using measures of recalled adversity. While, as noted, uncertainties remain about determinants of these

memories, evidence suggests that they constitute important liabilities for ill health and are an adequate base for new research on prevention. A second avenue would focus on individuals that are highly likely to have sustained actual exposure to ELAs as determined by contemporaneous, prospective measurement.

Strategy one: Ameliorative prevention in established illness using retrospective ascertainment

One area where the measures of recalled adversity have immediate importance is for the prevention of a malignant course or resistance to treatment in individuals already diagnosed with disease. For example, in the mental health field, recalled adversity predicts both a malignant course and resistance to treatment for major depression and a malignant course for bipolar illness (Agnew-Blais & Danese, 2016; Nanni, 2012). Similar investigations are just beginning in more general medicine. For example, recalled adversity is associated with poor response to bariatric surgery and may be associated with greater pain and treatment refractoriness in migraine (Lodhia et al., 2015; Tietjen, 2016). Taken together, these data suggest a program of research that should bring useful results rapidly. Two answerable questions are pressing: is recalled adversity a liability for malignant course and treatment resistance for a broader range of prevalent psychiatric and medical disorders? If so, are novel treatments required for those who recall ELA versus those with the same condition who do not? These findings suggest that recalled ELA may represent a critical individual difference factor important for tailoring treatments and monitoring adherence and should be assessed in clinical trials to better understand differential treatment response. For example, some patients with depression have elevated indices of chronic inflammation and respond selectively to antidepressants that target downstream effects of inflammation on brain metabolism (see: Haroon & Miller, 2017, for a review). Prospective data, from a longitudinal study assessing ELAs in childhood, suggest that ELA is distinctively

associated with the subset of depressed individuals with elevated indices of inflammation (Danese et al., 2008).

Strategy two: Targeting risk mechanisms in adults to prevent disease onset

Next steps towards prevention may be most advantageously pursued using samples with a high probability of containing children actually exposed to adversity in contrast to those who recall it, accurately or not, years later. This program of research has several components: selecting samples for study, defining targets for intervention, and selecting outcomes to test the efficacy of preventive interventions.

Tractable samples. The field has already drawn heavily on a small number of prospective samples where subjects have been followed into adult life (e.g., Barnes et al., 2009; Danese et al., 2009; Widom et al., 2012), but our Network's review (Network on Reversibility, 2016) has identified at least 12 other underutilized cohorts, some of which may be amenable to additional data collection. In addition, a sample of high-risk twins, on whom ELA exposure was carefully and contemporaneously documented, is entering adulthood and will soon be a valuable resource (Jaffee et al., 2013). Likewise, children - such as those at the Mt. Hope Center studies - where maltreatment and its short-term impact were meticulously ascertained have reached or will soon reach adulthood. The same is true of children in samples with varying length of time in institutional care from birth on (e.g., Rutter & O'Connor, 2004), although caution must be taken to select samples where institutional care entailed severe deprivation (Woodhouse, Miah, & Rutter, 2017). In addition to these samples, long-term follow-up of children with ELAs who were randomly assigned to ameliorative or preventive interventions will be of continuing value, although the strongest mechanistic evidence for malleable targets will derive from interventions that focus narrowly on specific risk mechanisms, i.e. putative treatment sensitive intervention

targets associated with the embedding or persistence of risk from ELA such as adverse parent-child relationships (e.g., Brody, Yu, Chen, Beach, & Miller, 2016; Stronach, Toth, Rogosch, & Cicchetti, 2013), rather than from broad-based, multimodal interventions (e.g., Campbell et al., 2014; Nielsen et al., 2018).

Animal models will also play an important role in clarifying causal pathways between ELA and later sequelae in adulthood, though we cannot characterize here the breadth, scope, and utility of these models. For example, rodent models have clarified gene expression mechanisms that link impaired maternal care (low licking and grooming) to stress reactivity and behavioral constraint in adult animals, and demonstrated the reversal of those effects with agents targeted at gene expression mechanisms (Champagne & Meaney, 2007). Monkey models provide more compelling behavioral homologues to human development and are a critical part of building a network of evidence on causality because individuals can be assigned at random to various levels of adversity. Monkeys can be randomly assigned to rearing conditions in the first months after birth (Conti et al., 2012) or, with equal facility, to positions of social power in hierarchical troops (Snyder-Mackler et al., 2016).

We anticipate at least three immediate uses for these human and animal cohorts. First, human cohorts identified by prospective assessment will offer solid data for validating improved methods of retrospective ascertainment. Second, they will help to clarify risk mechanisms in the causal chain. And finally, a few may be amenable to subsampling for experiments or micro-trials to test the malleability of those mechanisms. For example, considering a possible pathway from prospectively ascertained ELA to insulin resistance in adulthood, a micro-trial might test whether standard treatment for insulin resistance is equally effective in individuals with and without a documented history of ELA. Parallel work in existing adult samples with retrospective

assessment will offer a triangulation of evidence, and/or help clarify the differential pathways by which prospectively and retrospectively assessed ELA predict adult health and identify potential intervention targets along these pathways.

Defining targets. As noted, Power and Hertzman distinguished between critical period (“latency” in their terms) and pathway models to help define prevention strategies.

1) Critical period models. We are gaining insight into mechanisms of neural plasticity that explain why some adversities in early life have such a profound impact across the life span. These insights also hold potential for enhancing the effectiveness of interventions at midlife. Described in detail elsewhere, (Bavelier, Levi, Li, Dan, & Hensch, 2010; Werker & Hensch, 2015), molecular brakes control both the onset and termination of critical periods of openness to the environment by their action on GABAergic parvalbumin cells that—in response to triggers that are now well characterized—facilitate neural growth and organization and, when inhibited, freeze that development. Thus, stimuli during the critical period can have a lasting impact on brain organization and function. A range of interventions may reopen windows of plasticity and, potentially, correct deficits stemming from ELAs. Recent studies in mice demonstrate the role of locomotion in restoring plasticity to the cortex through molecular mechanisms that block the braking action on cortical sensitivity, likely through direct action on the parvalbumin cells (Stryker, 2014). While molecular mechanisms have not been clearly delineated, a broad range of evidence suggests that exercise can restore cognitive function in sedentary older adults through stimulation of increased BDNF (Erickson et al., 2011), a protein that can induce neuroplasticity through action on parvalbumin cells, and regrowth of brain structures—such as the hippocampus—that ordinarily shrink with age. Exercise also improves mood and cardiovascular and metabolic health, suggesting broad-ranging benefits. More recently, research has explored

the effectiveness of neurofeedback, a procedure where subjects learn how to self-activate specific brain regions. Under normal circumstances, activation of the ventral tegmental area enhances hippocampal function and memory for more complex relationships and contexts (Murty & Adcock, 2017); preliminary data suggest neurofeedback can help human subjects to selectively activate this neural center, which plays a critical role in new learning (MacInnes, Dickerson, Chen, & Adcock, 2016). In addition to these induced changes, increases in neuroplasticity may occur naturally in adult life. For example, animal studies (Champagne & Curley, 2016) point to brain plasticity in mothers around the time of the birth of their first offspring. Leveraging the plastic potential of the adult brain to reverse or compensate for health risks due to ELA is a promising area of future research, with initial questions focused on demonstrating the malleability of specific risk mechanisms via plasticity-inducing manipulations.

In human development, there are critical periods for visual, auditory, and language development, and ELAs that result in severe disruption of normal eyesight or hearing during these periods will have lasting deficits when children are exposed to normal visual or auditory stimuli or language later in development. It is unclear to what extent most ELAs, such as severe maltreatment, have lasting effects by mechanisms analogous to visual and auditory loss in early childhood (for a discussion, see: Callaghan & Tottenham, 2016). To explore this possibility, research must ascertain with precision the developmental onset and the offset of the adversity, a task that is difficult for persistent adversities like poverty or adverse family environments. Further, even if the time of offset and onset can be determined, we require evidence of a persistent deficit despite the restoration of a favorable environment that might be expected to restore capabilities impaired by the adversity.

For example, in animal studies, impaired maternal care of a rat dam within a critical 7-day period after birth has lasting effects on her female pups' capacity to care for their own offspring, but this effect can be fully offset by rearing these offspring in enriched environments post weaning (Champagne & Meaney, 2007). In contrast, in human adoption studies by Michael Rutter and his colleagues (Kumsta et al., 2015; Sonuga-Barke et al., 2017), children reared in unfavorable institutional settings from birth, but adopted at various times into favorable adopting families, showed persistence of autism like behaviors, attachment deficits and attentional deficits through their most recent follow-up (age 22 -25); these deficits were not influenced by variation in the quality of adoptive rearing but were highly dependent on the length of institutional care, if institutional rearing was longer than 6 months. Thus, the period between 6 months and 42 months, the highest age for adoption in this sample, may constitute a critical period for acquiring specific social and attentional abilities. It may be impossible to acquire these skills later in development without special approaches to intervention.

Adoption designs are also useful for specifying the timing of adversity during prenatal development. For example, in a study of children adopted at birth, prenatal depression in birthmothers affected cortisol dysregulation on the pathway to depression in adopted children (Laurent et al., 2013). In a further refinement of the adoption method, using children conceived by in vitro fertilization, Lewis and colleagues (2011) showed that maternal depression was associated with children's depression regardless of whether the mother's own (genetically-related) or a donated (not genetically related) ovum was fertilized. Taken together, these two studies provide strong evidence that exposure to maternal depression, very specifically in the prenatal period, has a causal relationship to subsequent behavioral development.

2) *Pathway models*. The allostatic load model noted above has been elaborated by a growing literature on the range of metabolic changes that follow from ELA. For example, Rasgon and McEwen (2016) have reviewed animal and human research documenting links among severe and sustained stress, elevated glucocorticoids and amino acids, chronic inflammation, and insulin resistance, with ultimate effects on reduced brain plasticity, all of which, to a point, are reversible by a range of interventions from exercise to dietary restriction. Because these pathways can be initiated in the pre-conception phase (Godfrey et al., 2017), as well as at various stages in fetal and child development, a constantly improving map of these interrelationships will offer multiple opportunities for preventive interventions. Pathway models are also important for linking early adversity to health outcomes via cognitive pathways and related outcomes such as education (Power and Hertzman, 1997) or behaviors that impair self-regulation and care, increase risk-taking, or lead to disrupted social relationships (e.g., Colman & Widom, 2004). Indeed, research on neuroplasticity, noted above, may be particularly useful in interventions directed at these behaviors: enhanced neuroplasticity, through such strategies as exercise or neurofeedback, may increase the effectiveness of preventive interventions aimed specifically at self-regulation, risk-taking, or disruptive patterns of social relationships.

Although pathway models are complex, they may provide a broader range of potential intervention targets at various points across the lifespan. However, even when tested in carefully conducted longitudinal studies spanning childhood and adulthood—with repeated assays across time—there are two major threats to their validity. First, the validity of these models may be confounded and the confounds may become more abundant as the complexity of pathway models increases. This is tractable problem if the *potential confounds are known and measurable*. In these circumstances, many investigators have turned to analytic strategies--such

as directed acyclic graphs-- to clarify not only the mediating and moderating steps linking childhood factors with adult health; these models incorporate as many potential confounders as possible (e.g., Kamphuis, Turrell, Giskes, Mackenbach, & van Lenthe, 2012).⁴

A second threat comes from unmeasured confounders; the most important may be genetic. The confounding arises because genetic factors can influence measures of environmental adversity (see review: Kendler & Baker, 2007) as well as measures of health status, and hence can account for some or all of the covariance studied in both pathways and critical period models. For example, South and colleagues (2015), using a large twin subsample of the MIDUS study, found that virtually all of the observed association between recalled childhood adversity and self-reports of current health were accounted for by genetic influences common to both. Comparable findings, using twin studies, have been reported for associations of adversity measures with childhood neurodevelopmental disorders (Dinkler et al., 2017) and adult criminal behavior and violence (Forsman & Langstrom, 2012), but not for ADHD symptoms in adults (Capusan et al., 2016). Adoption studies are useful here as well: in a longitudinal adoption study, parental depression was associated with adolescent and young adult psychopathology in a sample of biological parents rearing their own children and in adopted parents and their adopted children, suggesting environmental causality; however, the link between parental alcoholism and psychopathology was found only for children reared by their biological parents, suggesting that this association was due to genes common to parents and children (King et al., 2009; Marmorstein, Iacono, & McGue, 2012).

⁴ “Acyclic” models assume that variables in the model are sequentially linked across the lifespan with little or no recursive relationships at any point and are useful for outlining initiating variables, mediators and moderators, outcomes and variables that may serve to confound any of these relationships

Selecting outcomes for preventive intervention trials. A major problem confronting preventive research on cohort studies over extended periods is the long-time gap between ELA and the specific health outcomes to which it has been linked. We have already noted the utility of the allostatic load model to search for early indicators of embedding of ELAs. Extensions of this model provide many potential mediators between ELA and health outcomes, such as chronic inflammatory states and insulin resistance that appear later in life. These markers that anticipate later disease represent useful intermediate outcomes of preventive interventions.

Recent research offers new approaches to measuring fundamental processes of premature biological aging, some of which can be detected in early adulthood and are, in turn, related to a range of health outcomes that have been linked to ELA. Like allostatic load and other indices, measures of these aging processes may constitute potential outcomes for intervention research; they may appear earlier in development and hence provide valid outcome measures that reduced the time gap between intervention and outcome. For example, Belsky and colleagues (2015) summed changes in 18 biomarkers—including telomere length, HbA1C, triglycerides, mean arterial pressure and BMI, from ages 26 to 38 to compute a pace of aging score. Many of these measures overlap those drawn from the allostatic load model but, measured over several time periods, they add *rate of change* that may increase their precision as predictors of a broad range of health outcomes. This rate of change score correlated with other aging indicators such as grip strength, retinal arterioles, and older facial appearance, and was anticipated by adverse child experiences, such as lower SES and diminished child health, but also by a potential genetic indicator: age of longest-lived grandparent. Using a comparable strategy, Horvath (2013) identified 353 CpG sites whose methylation correlated with chronological age. Individual variation in methylation at these sites allows computation of “methylation age” that has been

associated with all-cause mortality (Chen et al., 2016). Horvath reports that this methylation aging score is 100% heritable in infants but declines to 39% in older individuals suggesting increasing environmental influences. Indeed, Brody and colleagues (2016) have presented preliminary data that parental depression—a presumed stress for their children--anticipates methylation age in adolescents that can be offset by intervention to reduce harsh parenting by these parents.

Taken together, data on allostatic load, pace of aging, and methylation clocks suggest that evaluating efficacy of preventive interventions in healthy adults to forestall medical disorders need not endure the many years between intervention and the emergence of the disorders selected for study. Biomarkers of multi-system dysregulation and aging may be a valid, near term outcome for randomized trials.

CONCLUSION

Human and animal research is establishing clear links between ELA and poor health in adulthood. Basic research in behavioral and physical development is clarifying targets for preventive intervention in adults to offset the risks of ELA. Retrospective accounts by adults of their ELA has helped distinguish subgroups of adult psychiatric patients that will have a malignant course and be treatment resistant. Research on the specific treatment needs of this subgroup is both promising and urgent. Equally urgent is research on whether recalled ELA has similar significance for medical disorders. Research on the prevention of ill health, originating in ELA, will be facilitated by a greater use of cohorts where ELA has been documented in childhood. Effective trials will identify and target potentially malleable behavioral, psychological, or neurobiological processes that can reverse or compensate for the persistent risk

due to ELA, utilizing current research on the effects of ELA on risky behavior, metabolic and inflammatory processes neurodevelopment and neuroplasticity.

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